CHIRON

Statement Presented To

Committee on Aging

United States Senate

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Introduction

Mr. Chairman, Members of the Committee: Thank you for the opportunity to provide a statement to the Committee on Aging at today's hearing. I am Howard Pien, president and CEO of Chiron Corporation, a global biotechnology company headquartered in Emeryville, California with 2003 revenues of $1.75 billion. Founded in California in 1981, Chiron is composed of three business units: BioPharmaceuticals, Blood Testing and Vaccines. Chiron is dedicated to research and innovation addressing global public health challenges. Through Chiron's breakthrough research discoveries in the fields of hepatitis B virus, human immunodeficiency virus and hepatitis C virus, millions of potentially fatal infections have been prevented.

Overview of Chiron

Chiron is the fifth-largest vaccines producer in the world, with sales of $678 million in 2003. Chiron Vaccines produces pediatric and adult vaccines to prevent life-threatening illnesses. These vaccines, which are sold throughout the world, have protected millions of people globally from *N. Meningitidis* Group C, polio, measles and other potentially fatal diseases. Chiron is a leading supplier of oral polio vaccine, producing more than 800 million doses annually to support global polio eradication efforts. Our rich heritage in vaccines is traced to the three European manufacturers Chiron has acquired over the past two decades, all of which were founded 100 or more years ago. The company has production facilities in Liverpool, United Kingdom; Siena, Italy; Marburg, Germany; and Ankleshwar, India; and it carries out research in Siena, Marburg and Emeryville. Chiron has a successful record of product development, including the launch of the first recombinant vaccine against pertussis, the first adjuvanted influenza vaccine and a conjugate vaccine against *N. Meningitidis* Group C.

Chiron currently has two vaccines licensed in the United States: Fluvirin® influenza vaccine, one of only two injectable influenza vaccines approved by the U.S. Food and Drug Administration (FDA), and RabAvert® rabies vaccine, approved by the FDA in 1997. Fluvirin® is indicated for immunization against the influenza vaccine strains contained in the vaccine for persons of 4 years of age and older. Chiron also supplies diphtheria and tetanus (DT) concentrate to GlaxoSmithKline for use in its DT-containing vaccines licensed by the FDA.[1] In addition, Chiron has initiated Phase III studies in the United States with the aim of licensing its conjugate vaccine against *N. Meningitidis* Group C, Menjugate®.[2]

Chiron and Influenza Vaccines

Chiron's $878 million acquisition of PowderJect Pharmaceuticals and its influenza vaccine Fluvirin in July 2003 represents a major commitment to ensuring that an adequate supply of vaccine is available to meet the needs of the United States. The principle driver for the acquisition was Fluvirin, produced at the company's FDA-licensed facility in Liverpool. Approximately 90 percent of the production from the facility is delivered to the United States, with most of the remainder going to the United Kingdom.

[1] Infanrix (DtaP) & Pediarix (DtaP-HepB-IPV)

[2] Menjugate® has been licensed in Europe via the Mutual Recognition Procedure and is also approved in other countries, including Canada and Australia.

Prior to its acquisition of PowderJect, Chiron was the third-largest producer of influenza vaccines globally and the second-largest supplier of influenza vaccine outside the United States. Today, Chiron is the second-largest producer of influenza vaccines in the world, with production of approximately 85 million doses annually. Chiron produces influenza vaccines at its facilities in Liverpool, Marburg and Siena and offers a number of influenza vaccines.

The acquisition of PowderJect represented a change in strategy for Chiron. Prior to this event, Chiron was unable to commit the resources required to enter the U.S. influenza market. However, over the last few years, significant changes in the dynamics of the U.S. influenza market have occurred. The key changes are:

- The recommendations of the Advisory Committee on Immunization Practices (ACIP) on influenza immunization were broadened to include individuals between 50 and 64 years of age and healthy children between 6 and 23 months of age, significantly expanding the potential market for influenza vaccine.
- Pricing of influenza vaccines has reached a level that allows manufacturers to invest in maintaining facilities to meet FDA standards and in expanding manufacturing capacity in order to meet increased demand.
- Reimbursement rates for providing influenza injections have been increased to levels at which physicians are encouraged to proactively immunize patients.

These changes in market dynamics were key factors in Chiron's decision to acquire PowderJect and expand its strong presence in the influenza market to include the United States. The shift in dynamics has also had a significant impact on investment decisions and capacity. Over the past five years, investments of approximately $70 million in both primary (bulk) and secondary (fill/finish) manufacturing have been made to increase the production capacity of the Liverpool facility. This investment was reflected in the purchase price of PowderJect and it has resulted in a significant increase in the amount of Fluvirin® supplied to the United States. The amount of Fluvirin® supplied to the United States on an annual basis more than quadrupled from 12 million doses in 2000 to 46-48 million doses in 2004, in addition to a two million dose supply for the Centers for Disease Control and Prevention (CDC) strategic reserve.

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Building on recent investments to increase manufacturing capacity at the Liverpool facility, Chiron is committing an additional $100 million dollars to replace its existing influenza bulk manufacturing facility with a new "state of the art" facility[3] to complement the secondary manufacturing facility opened in 1998. This commitment is being made to ensure that Chiron is in a position to continue to supply Fluvirin to the United States and to add incremental capacity until sufficient cell-culture production capacity is available to meet the market needs in the United States.

It should be recognized that changes in market dynamics, specifically the increase in price that has occurred over the past three years, have reversed the trend of decreasing manufacturing capacity. Producers are investing in capacity increases, upgrading facilities and licensing cutting-edge technologies for the U.S. market. Chiron

[3] A new fill/finish facility was completed a few years ago.

manufacturing investments are not unique in the industry, suggesting that the growing U.S. influenza market is an important public health priority that the private sector must ensure is addressed. However, given the nature of biologics manufacturing there is inevitably a lag between the decision to invest and improved capacity as a result of that investment. The United States is only now beginning to see the impact of the positive changes in market dynamics that occurred a few years ago with regard to expanded investment in manufacturing capacity.

Influenza Vaccine Production

Currently, all influenza vaccines marketed in the United States are produced in embryonated hens' eggs from designated chicken flocks. Individual lots of each of the three virus strains are grown in the eggs and harvested. The harvested virus is inactivated (killed), purified and separated from the egg proteins, usually by high-speed ultra-centrifugation. The whole virus concentrates are then further purified and split (split vaccine) or purified, as for Fluvirin, such that the vaccine contains predominately only the hemagglutinin and neuraminidase virus coat proteins (surface antigen or sub-unit). The monovalent (single-strain) antigen lots are sterile-filtered and quality control and potency tested. The monovalent lots are then formulated into trivalent vaccine (following FDA release), filled into the final containers and packed. The final run of primary antigen production in eggs is usually completed by September to allow time for processing, FDA potency assignment, vaccine formulation, packaging, quality assurance release and shipping to have completed release of the product into the marketplace by October or November.

In addition to its conventional egg-based influenza vaccines, Chiron is pursuing development of a cell culture–based subunit influenza vaccine using the Madin-Darby Canine Kidney (MDCK) cell line. Chiron's influenza cell-culture research program has completed Phase II clinical trials, with licensure in Europe projected sometime during the latter half of the decade. A Chiron influenza cell-culture production facility for full-scale production of the vaccine exists in Marburg. Chiron has submitted an Investigational New Drug Application to the FDA and is committed to licensure of its influenza cell-culture vaccine in the United States.

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While there do not appear to be significant clinical advantages to cell-culture vaccines as compared with the current egg-based vaccines in terms of safety and efficacy, the cell-culture production process offers several potential advantages. The overall process is more flexible and can be more easily adapted to increases in market demand. Additionally, the fermentation process is a closed system highly compliant with Good Manufacturing Practice (GMP).

In the event of an influenza pandemic, the cell-culture production process offers the promise of significant benefits compared to the conventional process, including:

- Cell culture production allows increased production capacity via faster initiation of continuous manufacture.
- Cell culture production is not dependent on a supply of eggs, which could be a key rate-limiting step in meeting an urgent public health crisis. Production can start at any time and can easily be expanded to full-year production.
- Cell culture production can reduce lead-time by six to eight weeks.

- Cell-culture production, unlike egg-based production, is a closed process that can be easily upgraded to Class III bio-safety standards that may be required for the management of a pandemic strain.
- Cell-culture production is suited to producing vaccines for influenza of avian origin, which will not grow on eggs without genetic modification.

Overview of Egg-Based Influenza Vaccine Production

Influenza vaccine usually contains three different influenza strains that are recommended by the World Health Organization (WHO) and the FDA. The WHO and the FDA select the influenza strains and industry's role in the public health partnership is to manufacture the designated product. From continuous surveillance by the WHO and the FDA, select strains to match the families of influenza viruses expected to be circulating each winter. The vaccine has a new composition each year, and the vaccine therefore cannot be stockpiled but must be made to order annually. In addition, influenza vaccine is a seasonal product, with the majority of immunizations occurring in the September-to-November time frame in the United States. If there is surplus vaccine that is unused at the end of the season, it cannot be reused the following year and must therefore be destroyed. The requirement for Southern Hemisphere influenza vaccine in the January to March season is comparatively small and usually of a different composition.

Vaccine manufacturers try to match annual supply and demand, ensuring enough doses are available to meet demand while avoiding wasteful destruction of unused vaccine at the end of the season. The inability to carry over inventory into the following season means that the margin of error is much smaller than for other vaccines. Forecasting demand accurately is complicated by the fact that it is not possible to assess the severity of the epidemic and then adjust production volumes; additional capacity cannot be added at short notice and must be planned at least one season in advance. In fact, almost all the influenza vaccine manufacturing is completed before the influenza season begins. The cycle time for vaccine production means that demand must be predicted based on historical data, without an indication of the severity of the current influenza epidemic.

Supply of Influenza Vaccine for the 2004/2005 Influenza Season

On August 26th, Chiron Vaccines announced that in conducting final internal release procedures for its Fluvirin® influenza virus vaccine, our quality systems identified a small number of lots that did not meet product sterility specifications. Chiron therefore announced that it had delayed releasing any Fluvirin® doses until it had completed additional release tests, a process that will delay release until October. As of September 27th, it remains Chiron's expectation that between 46 million and 48 million Fluvirin® doses will be delivered to the U.S. market beginning in early October as compared to the 50 million doses projected in July. Since the original announcement Chiron has worked closely with key stakeholders[4] to keep them abreast of the status of the testing. The planned late-season delivery of 2 million Fluvirin

[4] Chiron has held regular updates on the supply situation via teleconference with representatives from the CDC, National Vaccine Program Office, Advisory Committee on Immunization Practice, American Academy of Family Practitioners, American Academy of Pediatrics and the American Medical Association

doses for a national stockpile held by the U.S. Centers for Disease Control and Prevention (CDC), not included in the totals above, remains on schedule. The results of the tests are entirely in line with the company's expectations that the variance was confined to the initial scope identified. Following compilation and formal sign-off of the test data, Chiron expects to report its conclusions to regulatory authorities and, upon confirmation, proceed with releasing Fluvirin® to the U.S. market in early October.

As October and November are the primary months when influenza vaccine is given, the impact of the delay on the 2004-2005 influenza vaccination season should be minimal. Furthermore, as in past years, CDC urges continuation of Influenza vaccination into December and beyond if vaccine is available and therefore ample time will exist to immunize individuals at risk from the disease. Chiron is extremely proud of the dedication displayed by its staff in working continuously these past few weeks to develop and execute the formal retest program making possible the delivery of a safe and effective vaccine in time to for the influenza season.

It is important to note that the 46-48 million doses of Fluvirin® projected for delivery during the 2004 /05 influenza season represents an increase of more than 25% compared to the amount of influenza vaccine Chiron supplied to the United States last season. Overall, the CDC estimates that there will be roughly 100 million doses of influenza vaccine available[5] representing an increase of approximately 15% compared to the 87 million doses of influenza vaccine available last season. In addition, in response to the supply shortage that occurred last year, the CDC has worked with influenza vaccine manufacturers to establish a ***"strategic reserve***" of over 4 million doses of influenza vaccine delivered in November and December. Chiron, as mentioned previously, will deliver two million doses to the late season stockpile. Chiron welcomed the opportunity to work collaboratively with the CDC to develop the program securing a strategic reserve that did not create the unintended consequence of detrimentally impacting the private market. Therefore, despite the delay in availability of Fluvirin®, it does not appear that there will be a shortage of influenza vaccine this season as manufacturers will be supplying the United States with 13 million doses more than last year.

The key challenge for the 2004/05 influenza season will most likely not be managing a supply shortage but, rather, ensuring that all of the doses of influenza vaccine produced end up in the arms of individuals. Last year a milestone was reached: The estimated 83 million Americans immunized represented the highest immunization rate ever for influenza and almost all the injectable inactivated influenza vaccine was used. Prior to 2003, immunization rates had remained relatively static, and unused vaccine had to be destroyed. For example, it is estimated that approximately 12 million doses were destroyed in 2002. Therefore, despite the delay in availability of vaccine, ensuring that demand exists for the additional influenza vaccine available this season is crucial in the context of planned increased production capacity for future seasons. If demand this season remains static, or returns to levels seen in 2002, supply will again exceed demand. Depending on the magnitude of the shortfall in demand it may lead to a reduction in supply in future years as supply of the vaccine is closely aligned with projected demand based on historical trends. Influenza

[5] Inactivated influenza vaccine and live-attenuated vaccine

immunization stakeholders in both the public and private sector are working together on activities to reassure the general population about the availability of vaccine, encourage influenza immunization and attempt to extend the influenza immunization season into December.

In summary, as mentioned previously, 2003 represented the highest number of people ever immunized, and there is no guarantee that the same levels will be achieved in the event of a less severe epidemic or a public perception of a supply shortage. We should therefore not be complacent and assume that because excess demand existed in 2003, it will automatically spill over and absorb the additional 13 million doses that will be available this season.

Protection of the Aging Population Against Influenza

Vaccination of persons at risk from the complications of influenza is a key public health strategy in preventing morbidity and mortality in the United States. The influenza epidemic is an annual event, which was estimated during the 1990s to have caused an average of approximately 36,000 deaths annually and 114,000 hospitalizations in the United States with 90% of the mortality occurring in adults aged 65 years of age and older[6]. A more recent study has suggested that the rate of hospitalizations related to influenza may be even higher with over 200,000 hospitalizations occurring annually[7]. Over the last decade the United States has had success in raising immunization coverage rates for individuals above 65 years of age. Data analyzed from the Behavioral Risk Factor Surveillance System (BRFSS) in 1993 indicated that 50% of respondents reported having received influenza vaccine compared to 66% in 2002[8]. This represents significant progress but is still below the 90% goal set for non-institutionalized adults in the Healthy People 2010 Objectives[9] and has remained level since 1997[10]. Continued investment in patient education and ensuring access to vaccine will be required if coverage rates are to continue to increase for individuals 65 years of age and older. Achieving higher coverage rates will increase in importance over the next few years as influenza is expected to have an increasingly serious impact in the United States due to the aging population. Therefore having effective strategies in place to prevent the disease through immunization will become increasingly important if the burden of disease is not to increase.

In addition to strategies that increase awareness of the need for prevention and access to the vaccine, setting appropriate reimbursement rates for vaccine purchase and administration is important, particularly through Medicare. The majority of the population 65 years of age and older receive vaccine from their primary health care provider and therefore ensuring incentives are in place for providers to actively immunize patients is important. The increases in the administration rates in 2003 by the Centers for Medicare and Medicaid Services (CMS) by roughly 90% to between

[6] Source: Morbidity & Mortality Weekly Report 2003, Vol. 52 RR8
[7] Source: *JAMA.* 2004;292:1333-1340
[8] Source: Morbidity and Mortality Report 1996, Vol 45 No 40; Morbidity and Mortality Report 2003, Vol 52 No 41
[9] Objective no 14.29 at www.health.gov/healthypeople/
[10] Source: Morbidity and Mortality Report 2003, Vol 52 No 41

six and eight dollars from less than four dollars has served to encourage physicians to actively seek out immunization in their population.

In addition to adequate administration fees, maintaining reimbursement rates that accurately reflect the acquisition cost of influenza vaccine creates an incentive for physicians to acquire the vaccine. In recognition of this, the Senate provided leadership in crafting the Medicare Modernization Act to ensure that influenza vaccine would be reimbursed at 95 percent of the Average Wholesale Price (AWP) and, equally important, that the Center for Medicare and Medicaid Services (CMS) continue its current practice and update this reimbursement rate on a quarterly basis. We understand that CMS will be sending a Transmittal to the Medicare Carriers reflecting this policy by the end of the month. Any change to the current reimbursement system will have a negative impact on coverage rates if it leads to a reduction in reimbursement for physicians. By setting adequate reimbursement rates and administration fees CMS has created an incentive for physicians to actively immunize their elderly patients against influenza. Any future changes to MMA through legislation or regulation must not create a disincentive for physicians to actively immunize their patients.

Individuals aged between 50-64 years old are another population that benefit significantly from influenza immunization as this population has an increased prevalence of high-risk conditions. In 2000, approximately 42 million persons in the United States were aged 50–64 years, of whom 12 million (29%) had one or more high-risk medical conditions. In 2000 the Advisory Committee on Immunization Practices (ACIP) broadened the universal recommendations for influenza vaccine to include individuals between 50-64 years of age because of the prevalence of high-risk conditions in this group. Influenza vaccine was recommended for this entire age group to increase the low vaccination rates among persons in this age group with high-risk conditions. Age-based strategies are more successful in increasing vaccine coverage than patient-selection strategies based on medical conditions. In addition, individuals aged between 50 and 64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and reduced need for medical visits and medication. For example a reduction in the use of antibiotics to which antimicrobial resistance is an increasing problem. Furthermore, fifty is an age when other preventive services begin and therefore the timing is appropriate.

Despite the universal recommendation being in place for several seasons only 36% of respondents between 50-64 years of age in the 2002 BRFSS reported having received influenza vaccine during the previous 12 months, well below the level of respondents above 65 years of age. Significant efforts need to be invested in reaching this age group for the following reasons. First, as stated in the previous paragraph, roughly one third of the individuals in this age group are estimated suffer from conditions such as chronic disorders of the pulmonary or cardiovascular systems, including asthma and metabolic diseases such as diabetes that put them at higher risk of complications due to influenza. Second, in the longer term, achieving high influenza coverage rates in this age group will translate to future higher coverage rates in the 65 and older population. It is likely that an individual who is in the habit of getting an annual influenza vaccine is likely to continue to do so as they age.

Chiron believes that substantial and innovative efforts need to be undertaken to raise influenza immunization coverage rates in individuals aged 50 and above. Specific efforts should be targeted at reducing disparities between geographic areas and racial / ethnic groups. For example, coverage rates are lower for Hispanics and non-Hispanic blacks as compared to non-Hispanic whites[11]. The variation in influenza vaccine coverage observed among geographic areas suggests that opportunities exist to apply lessons from high coverage areas such as the New England States to raise rates in low coverage areas. These efforts can have the biggest impact through collaboration between the public and private sector. Chiron believes that key stakeholders (manufacturers, distributors, the public health community, providers and insurers) should form public private partnerships to address the following:

- Raising awareness of the immunization recommendations among the medical community and general population.
- Dispelling some of the myths about influenza vaccine that exist ***(I can get influenza from the vaccine)***
- Encouraging immunization by highlighting the benefits of immunization and developing innovative programs for facilitating access to the vaccine.
- Extending the immunization season into December to ensure all doses are used and to potentially increase the window in which vaccine could be supplied to the market.

These efforts must not be limited to the coming influenza season but need to be continued for the long term if the Healthy People 2010 goals of 90 percent coverage rates of non-institutionalized adults 65 years of age and older and 60 percent coverage rates of high-risk non-institutionalized adults 18-64 years of age are to be attained.[12] While these goals are ambitious, they are achievable if both the public and private sector join forces in a multi-year effort. The National Influenza Vaccine Summit organized by the American Medical Association in collaboration with the CDC that brings together key stakeholders in the private and public sector is a vehicle that is already working on these goals and Chiron is actively involved in the Summit and believes it can provide the leadership required to champion initiatives aimed at raising coverage rates for influenza. The success of such partnerships in raising immunization rates for pediatric vaccines demonstrates how this approach can achieve positive results. It is recognized that there are differences between influenza vaccination and the pediatric immunization situation, where school entry mandates played an important role in raising coverage rates. Nevertheless, it is felt that some of the lessons learned would be applicable.

Immunization of contacts of high-risk individuals represents an additional strategy for protection of persons at high-risk for complications from influenza. Persons who are clinically or sub-clinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might therefore might cause a reduction in influenza-related deaths and hospitalization among high-risk populations. Health-care workers (HCWs), due to the nature of their occupation, are often in contact with high-risk individuals and therefore the ACIP and other major

[11] Source: Morbidity and Mortality Weekly Report Vol. 52 no 41.
[12] The target rate for institutionalized adults aged 18 and older is 90 percent.

medical groups and nursing organizations have recommended that HCWs should be vaccinated against influenza. Despite the recommendations coverage rates among HCWs are less than 40%[13]. Chiron believes that significant efforts need to be devoted to increasing immunization coverage rates in this group. First, improving coverage rates will protect health-care workers, their patients, and communities. This will improve prevention, patient safety, and reduce the disease burden. Second, health care workers are an important source of information on immunization to the general population and must lead by example. An unvaccinated healthcare worker is not a credible advocate for immunization and therefore a first step to convincing the general public to get immunized against influenza is ensuring health care workers are vaccinated.

In order to raise coverage rates among health care workers Chiron believes the following is needed:

- HCWs should be provided with easy access to influenza vaccine
- Resources should be committed to institutionalizing immunization of HCWs in their workplace
- Professional health care organizations should develop policies to support HCW immunization and encourage constituents to educate HCWs about the benefits of immunization
- Health-care workers' influenza immunization rates should be regularly measured and reported.

In this context Chiron supports the recommendations made by the National Foundation of Infectious Disease in its call to action *Influenza Immunization Among Healthcareworkers* [14] and encourages professional health care organizations and institutions to follow them.

As Immunization of contacts of high-risk individuals represents an additional strategy for protection of persons at high-risk for complications from influenza, Chiron was pleased to see that the ACIP had added language to its Recommendations on Prevention & Control of Influenza stating that " *ACIP plans to review new vaccination strategies for improving prevention and control of influenza including the possibility of expanding recommendations for use of influenza vaccines"*[15]. At present roughly 60% of the United States population are covered by the recommendations as it is estimated that 185 million individuals fall into the required categories. Therefore moving to a universal recommendation is not that great a leap. The experience of the Canadian province of Ontario in implementing a universal recommendation is encouraging as coverage rates were increased in both the general population and in high-risk groups.

Pandemic Influenza

A universal recommendation for influenza immunization would offer significant benefits for pandemic preparedness, as it would increase demand and therefore the supply of influenza vaccine available in the event of a pandemic. An influenza

[13] Source: Morbidity & Mortality Weekly Report 2003, Vol. 52 RR8
[14] http://www.nfid.org/publications/hcwmonograph.pdf
[15] source: Morbidity and Mortality Weekly Report Volume 53

pandemic occurs when there is a major change (shift) in the influenza virus such that the majority of the world's population has not been previously exposed to the strain and is therefore extremely vulnerable to the virus. Influenza pandemic is a major public health threat with the potential to cause a rapid increase in morbidity and mortality. Three pandemics occurred in the 20th century, the first in 1918. It is estimated that approximately 500,000 deaths due to influenza occurred in the United States between September 1918 and April 1919 and that the pandemic caused 20 million deaths worldwide. The 1918–1919 pandemic was the worst pandemic recorded, and mortality in more recent pandemics has been lower. The Asian influenza pandemic of 1957 is estimated to have caused approximately seventy thousands deaths in the United States while the Hong Kong influenza pandemic of 1968 is estimated to have caused 33,000 deaths.

Immunization of individuals with a pandemic strain specific vaccine is likely to be the most important public health intervention for preventing morbidity and mortality from pandemic influenza. Therefore during the inter-pandemic period it is important to take the required steps to ensure that a pandemic vaccine can be developed as quickly as possible in the event of an influenza pandemic. Chiron welcomes the steps the National Institute of Allergy and Infectious Diseases (NIAID) has taken as part of the NIAID Influenza Pandemic Preparedness Plan to support the manufacture and production of a candidate vaccine against a pandemic strain of avian influenza. Chiron is contributing to this effort through participation in two projects. It is producing pilot lots of investigational H5N1 vaccine at its Liverpool facility using the production process used for its marketed flu vaccine, Fluvirin®. Chiron Vaccines will produce 8,000 doses of the H5N1 vaccine for the NIAID, who will conduct clinical studies exploring the safety profile and immunogenicity of two different doses. It is also producing pilot lots of an investigational vaccine based on an H9N2 at its Siena facility. Different dosages of the vaccine, based on an inactivated strain of the virus developed by the CDC, will be prepared. Some dosages will contain Chiron's MF59 adjuvant—a substance designed to boost the vaccine's protective effect. Chiron will first test the general safety of these different formulations in laboratory animals and, based on its findings, will then produce 4,000 single-dose syringes of each for clinical evaluation in healthy adults. NIAID will perform a Phase I trial, currently slated for early next year, to test the safety and effectiveness of each formulation in humans. Chiron believes that these sorts of partnerships are crucial to ensure the availability to the public of safe and effective vaccines against avian influenza as soon as possible and that additional investments should be considered once the results of these trials are available.

The draft Pandemic Influenza Preparedness and Response Plan recently published by the National Vaccine Program Office addresses the issue of pandemic vaccine research and development in the inter-pandemic period. Chiron supports the recommendations of the report on the enhancements that can be made to the vaccine development infrastructure during the inter-pandemic period particularly the creation of libraries of reassortant influenza viruses suitable as reference strains for vaccine production, the use of new molecular techniques such as "reverse genetics" to produce high growth reassortant viruses, evaluation and licensure of an influenza vaccine that includes an adjuvant and development of new technologies such as flu cell culture. In addition, Chiron believes that support for the research priorities outlined in the report will encourage investigation into the development of new

influenza vaccines that are not based on the current antigens or production techniques. This research may not only lead to a better pandemic vaccine but may also lead to a vaccine that provides better or longer term protection in the inter-pandemic period.

Vaccine Supply in a Pandemic

From the perspective of an influenza vaccine producer, planning for a pandemic represents a significant challenge due to the nature of influenza vaccine production. Essentially, the following factors limit the ability to rapidly expand supply in the face of a pandemic under current circumstances:

- **Production capacity**—Influenza vaccine production capacity is aligned with annual demand for vaccine under normal circumstances, i.e., between pandemics, and therefore little or no surge capacity exists to meet pandemic demand.
- **Inability to stockpile**—Stockpiling of vaccine in preparation for a pandemic is not a viable strategy, as it is not possible to predict the vaccine strain that will cause the pandemic.
- **Supply of primary production material**—Currently, vaccines are produced using eggs, and ensuring an adequate supply of eggs to significantly increase production during a pandemic represents a significant challenge.
- **Specialized production facilities**—Additional quantities of vaccine could not be readily produced in facilities used for other vaccines, as production and purification equipment and facilities are specifically designed for influenza vaccines.

In the event of a pandemic, Chiron will strive to fulfill its responsibility to supply vaccine to the United States and international markets. Chiron has plans to maximize production of influenza vaccine at its Liverpool, Marburg and Siena facilities to help overcome these challenges in the event of a pandemic. The following steps would be undertaken to increase vaccine production:

- **Year-round production**—Influenza vaccine production would be run continuously over the whole year as opposed to the current seasonal production cycle. However, it should be noted that this assumes that additional egg supply will be available to keep the facilities running year round.
- **Monovalent vaccine**—A monovalent vaccine containing the pandemic strain only would be produced as opposed to the standard trivalent vaccine containing three strains. Manufacturing capacity would therefore be increased by a factor of three, assuming that the vaccine contains the same amount of antigen as the conventional influenza vaccine.[16] Any increase in the antigen content of the pandemic vaccine would result in a proportional reduction in the number of doses that could be produced. At present, the clinical data available to support the definition of the pandemic vaccine is limited.

[16] It should be noted that studies of experimental vaccines produced in response to the avian influenza A outbreaks in Hong Kong suggest that a greater dosage or an adjuvanted vaccine may be required. Therefore, whether this assumption will turn out to be valid is open to question.

Chiron estimates that implementing these two steps in the event of a pandemic would more than triple its influenza vaccine manufacturing capacity, of which 50 percent would be produced at its FDA-licensed facility in Liverpool, assuming the pandemic vaccine contains the same amount of antigen as the normal vaccine. By the end of the decade, under its current plan, Chiron anticipates being able to increase its pandemic vaccine production by an additional 50 percent due to expanded production capacity in Liverpool and the availability of a cell-culture facility in Marburg producing its MDCK–based cell-culture vaccine.

It is important to note that the current regulatory approval process would have to be expedited in order for manufacturers to rapidly convert to producing a monovalent pandemic vaccine in a timely fashion. Under the present system, obtaining regulatory approval could be a bottleneck in supplying pandemic vaccine. Chiron believes that discussions and planning should occur now between manufacturers and the FDA in order to determine the regulatory pathway for approval of a vaccine, including any amendments to official release requirements in the event of a pandemic. This would be of significant value to expedite the availability of supply should the pandemic occur.

In the face of a potential influenza pandemic, switching production to a monovalent pandemic vaccine imposes a significant financial risk: If the predicted pandemic failed to materialize, there would be no demand for the monovalent vaccine, and Chiron would be forced to destroy the vaccine. Therefore, Chiron would be unlikely to make the decision to switch production from trivalent vaccine to a monovalent pandemic strain without a guarantee that its production would be purchased whether or not the pandemic materialized. Chiron would be unable to assume this risk without financial guarantees being in place due to the severe consequences of losing an entire year's revenues generated from the production of influenza vaccine. Therefore, in order to trigger a switch to pandemic vaccine production as quickly as possible in the event of a potential pandemic, governmental contract authority to purchase pandemic vaccine production by an agreed-upon mechanism of compensation should be in place prior to a pandemic. Such a contractual agreement between vaccine manufacturers and the government implies a limited role for the private sector in the marketing of a vaccine in the event of a pandemic. National governments will procure the vaccine, be responsible for its distribution and determine the priority of immunization. Based on these considerations, Chiron assumes that in the event of a pandemic, the market for influenza vaccine will be almost exclusively a public-sector market, with national governments purchasing vaccine from producers.

Chiron recommends that a mechanism for indemnifying manufacturers, similar to that for smallpox and swine flu, be established in advance of a pandemic situation. The United States Government must indemnify and hold harmless producers of influenza vaccine if they are to manufacture the vaccine in the event of a pandemic. Under section 304 of the Homeland Security Act of 2002, "covered persons," including manufacturers, are deemed to be PHS employees, so that the United States is the exclusively liable party under the FTCA for any injury or death arising out of the administration of a "covered countermeasure" against smallpox during an "effective

period" defined by HHS declaration.[17] It is vital that Congress enact a similar provision for manufacturers producing influenza pandemic vaccines.

Despite a potential increase in the supply of vaccine by a factor of greater than three, there will be a global shortage of influenza vaccine in the event of a pandemic. Demand for influenza vaccine would increase dramatically compared to normal circumstances due to the need to immunize most of the global population and a potential increase in the number of doses required per person to provide immune protection from one to two. Current global influenza vaccine production capacity, estimated at roughly 300 million doses in a typical year,[18] will most likely be unable to cope with global demand, and therefore a shortage of vaccine is expected to occur.

Chiron is committed to maintaining supply to the United States in the event of a pandemic. However the current location of Chiron's influenza manufacturing facilities outside of the United States imposes constraints on its ability to ensure this occurs, as it is not clear how global allocation of the vaccine will take place in the event of a pandemic. Where demand outstrips supply, it is possible that national authorities will impose constraints on the allocation of influenza vaccine by manufacturers under their jurisdiction. One of the constraints that may be imposed by national authorities is that producers be required to give priority to meeting national demand before shipping vaccine supply to traditional markets. For example, Chiron could be asked to give precedence to the United Kingdom in allocating vaccine supply from its Liverpool facility, as it is the only domestic source of supply for that country. Furthermore, once the needs of the United Kingdom were met, priority might be given to other European countries before allowing vaccine to be made available to the rest of the world. In addition, manufacturers with facilities located in European Union countries may be required by their national authorities to give precedence to the needs of other EU member countries once domestic needs have been met before vaccine can be exported outside of the EU, particularly for those member states that do no not have domestic production capacity. These variables are real and uncharted. Chiron believes it is important for the United States, United Kingdom and EU authorities to engage in discussions on pandemic influenza vaccine supply in advance of an outbreak in order to clarify supply priorities for its Liverpool facility and would welcome the opportunity to participate in the discussions.

The draft Pandemic Influenza Preparedness and Response Plan recently published by the National Vaccine Program Office also provides encouraging signs for increasing capacity. Chiron fully supports the statement contained in the document that *"Implementing strategies to increase annual vaccine demand and use during the inter-pandemic period will encourage manufacturers to respond with increased supply thus increasing production capacity which will contribute directly to pandemic preparedness"*. Chiron is committed to investing to increase its production capacity if demand for influenza vaccine in interpandemic years continues to increase. However, investment in increasing the supply of vaccine will follow increased demand.

[17] *See* 42 U.S.C. § 233(p)(1)-(2), (7).
[18] Chiron internal estimate.

In conclusion, an influenza pandemic will represent a significant challenge to Chiron, as it will need to rapidly expand influenza vaccine at the expense of other products in its portfolio. Recognizing this challenge, Chiron is committed to supporting global pandemic preparedness efforts prior to the inevitable occurrence of a pandemic. Chiron believes that over the past year the United States Government has taken significant steps towards addressing some of the key issues identified below and recommends that the Congress and the Public Health Service focus on the following critical priorities after the November elections.

- Strategic public education programs to increase demand for influenza vaccine during interpandemic years to assure increased supply of influenza vaccines from year to year, thus increasing supply in a pandemic situation.
- Research and development efforts to determine whether or not pandemic vaccine supply can be expanded by adjuvantation of the vaccine.
- Identifying the regulatory pathway for approval of a pandemic vaccine, including any amendments to official release requirements in the event of a pandemic, as well as assurance to manufacturers that there will be flexibility within the regulatory process to rapidly advance clinical trials to coincide with the influenza cycles so that clinical testing will not be delayed.
- Implementing mechanisms to trigger the switch to production of a monovalent pandemic vaccine, whether or not the pandemic materializes, through an agreed process.
- Establishing in advance of a pandemic situation a mechanism to indemnify influenza manufacturers and provide for a compensation program for recipients of the pandemic vaccine should it prove necessary.

In summary, Chiron has invested heavily in ensuring that the United States has a supply of influenza vaccine in inter-pandemic years, which will contribute to protecting the elderly against morbidity and mortality due to the disease. Chiron is committed to providing leadership in the U.S. influenza market. Chiron is shouldering the necessary risks to expand its ability to increase supply and is bringing cutting-edge technologies in influenza cell-culture production to the U.S. market. Fundamental to Chiron's success in realizing its commitments is the ability to work collaboratively with Congress, the Administration and public health officials to reach the immunization rates established in Healthy People 2010 while incentivizing the private sector to transition to new technologies in influenza immunization. These priorities are of critical importance if we are to effectively protect the population as it against influenza as it continues to age and position the United States for preparedness for a global influenza pandemic.

Thank you for the opportunity to present the views of Chiron Corporation. I am happy to answer any questions you may have for me.